Heterogeneity of airway hyperresponsiveness: time for unconventional, but traditional, studies

Airway hyperresponsiveness as “a morbid sensitiveness of the bronchial tubes, exalting a stimulant that should not be a stimulant” (16) has gone into its 3rd century. There is general consensus that this propensity to (more severe) airway narrowing should be regarded as a clinically relevant, functional characteristic that is central to our understanding of asthma. Multiple generations of outstanding investigators have made formidable efforts to unravel the pathophysiological pathways that are responsible for such less-well-adapted behavior of the airways. The recent series in this journal, “Airway hyperresponsiveness: from molecules to bedside,” exquisitely illustrates the level of sophistication that has been reached in our present attempts to disentangle the heterogeneous mechanisms of airway hyperresponsiveness.

Right from the very beginning, both the muscular and nonmuscular elements in the airways have been in focus in relation to airway hyperresponsiveness (16). Even though these two components are tightly interrelated in structure and function, there have been “schools” of thought promoting the role of airway smooth muscle on the one hand and airway wall geometry on the other as the primary and predominant cause of airway hyperresponsiveness. In general, “school” formation can be extremely stimulating for scientific progress. However, it also illustrates a relative immaturity of thinking, which is quite surprising for a 150 yr old. Even though the above schools have opened up and even merged by integrating the dynamics of muscular and nonmuscular elements (2, 10), the present debate still illustrates that we may not have used each of Koch’s traditional postulates strictly enough to examine the relative importance of the (interrelated) determinants of airway hyperresponsiveness. As we all know, the third postulate requires elimination of potential mechanisms, which is not only very troublesome (if feasible) in humans in vivo, but is equally demanding in animals models. Is there a way out?

In the present issue of the journal, Wagers et al. (17) are presenting an experimental model in allergen-sensitized mice in vivo, in conjunction with a computational model of the time course of changes in respiratory impedance following a single dose of inhaled methacholine. By using an iterative approach, the settings of the computational model were adjusted to match the experimentally observed changes in flow resistance of the conducting airways, plus the accompanying changes in tissue resistance and stiffness. This allows mathematical manipulation of various combinations of predetermined mechanisms to best explain the in vivo findings. Essentially, the study shows that a decrease in airway radius alone cannot adequately match the observed time course of the various components of impedance after methacholine. However, by increasing airway wall thickness plus the critical closure radius (propensity of airways to close), the computational model was able to better (but still not perfectly) fit the experimental data. The authors conclude that alterations in the geometry and mechanics of the airway wall are the most likely underlying mechanisms of airway hyperresponsiveness, as opposed to changes in smooth muscle shortening per se (17).

There is no doubt that this quantitative approach is highly informative on relative contributions among the heterogeneous mechanisms that are supposed to contribute to airway hyperresponsiveness. Particularly, the time course analysis seems to be an essential component when examining the response to inhaled bronchoconstrictor agents (5). However, the drawback of using time-response curves only is that information on the full dose-response curve is not taken into account, which is known to be essential when dissecting mechanisms of airway hyperresponsiveness (13).

Nevertheless, this study is an excellent attempt to integrate and to weigh muscular and nonmuscular aspects of airway narrowing during allergic inflammation. The findings regarding mucosal thickness are seemingly opposite to those recently reported in asthmatic subjects by using helical computed tomography scans (12). This may illustrate the importance of measuring each component of impedance, rather than resistance alone. Interestingly, the model’s emphasis on airway closure seems to fit in with recent observations in patients with asthma, showing an association between the tendency toward exacerbations and the lung volume at which airway closure occurs, as measured during clinically stable episodes (4). This might be secondary to changes in elastic properties of the airway wall, for which there is histological evidence in asthma (9). Model studies like the present one are highly suitable to weigh the importance of such pathological observations.

The authors are the first to highlight the limitations of their approach, by emphasizing that the outcome of the computational model essentially depends on the selection of parameters and the adequacy of the assumptions regarding their scaling and settings. Therefore, the study remains observational and cannot be regarded as hypothesis testing according to Koch’s third postulate. In that sense, the study is in good company, because many other modern research strategies, such as genomic and proteomic approaches, are merely observational and thereby hypothesis generating.

There are also specific limitations. The airway and lung inflammation in ovalbumin-sensitized mice may not be fully representative of the abnormalities in naturally occurring disease. The striking confirmation of this is the fully adequate normalization of resistance by two deep inspirations, which is notably impaired in humans with airway hyperresponsiveness (15). In addition, the inflammation and the accompanying geometric changes were not morphometrically measured in the present study, apart from one qualitative histological example. Airway wall thickness represents more than just epithelial thickness alone and may also have to include submucosal dimensions and airway-parenchymal coupling (8). When taking such detailed morphometric outcomes into account, Palms et al. (14) elegantly demonstrated in a rat model that prolonged allergen exposure is required to adequately describe the dynamics of hyperresponsiveness in relation to changes in airway wall thickness and extracellular matrix composition.

Has the present study provided sufficient evidence that perhaps airway smooth muscle does not contribute to airway hyperresponsiveness after all? No, it has not! The model did...
not include critical changes in smooth muscle growth, shortening velocity, stiffness, and length adaptation (2, 10), for which computational models are being developed (7). Combining such models should be a major step forward.

It can be envisaged that the relative contribution of the muscular and nonmuscular mechanisms of airway hyperresponsiveness will vary between, and even within, patients. Eventually, after 150 years, we have to move ahead toward (traditional) hypothesis-testing studies. This will require unconventional experiments. The first option may be to eliminate airway smooth muscle in vivo by thermal bronchoplasty (11), which has already reached human phase 2 studies. A second perspective is to potentially change the phenotype of, e.g., smooth muscle cells or fibroblasts, by homing of their progenitor cells into the airways (3, 6). And finally, are we not close to novel pharmacological interventions, such as those targeting the first three minutes: smooth muscle fragmentation of the elastic system in fatal asthma. Am J Respir Crit Care Med 160: 968–975, 1999.


REFERENCES


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